The IPLEX Experience in Italy

PROGRAM DESIGN

Insmed's Expanded Access Program (EAP) was established to provide IPLEX™ to physicians in Italy for the treatment of patients with amyotrophic lateral sclerosis (ALS) and to obtain information regarding the safety, tolerability and influence of IPLEX treatment on disease progression. This Program represents the first use of IPLEX in patients with ALS.

THERAPY

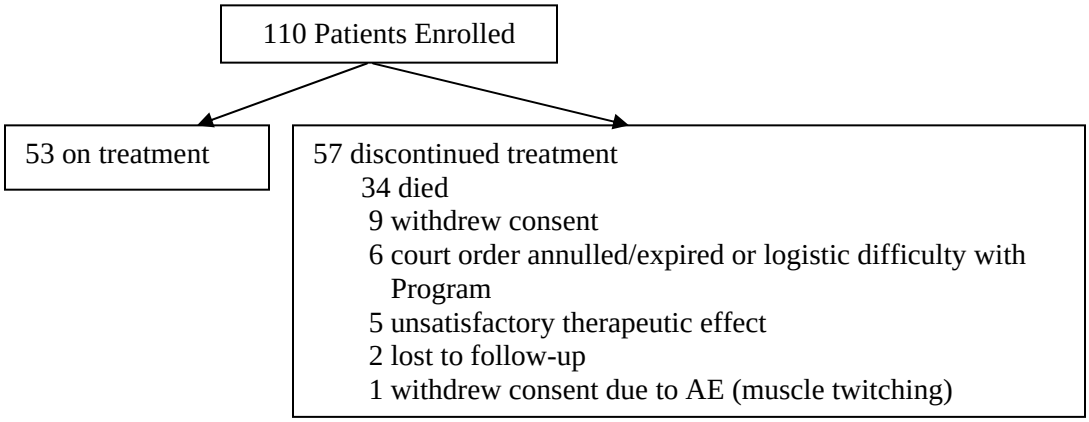
IPLEX is approved for the treatment of severe Primary IGF-I Deficiency in the United States and has been studied in various clinical settings for the treatment of myotonic dystrophy, HIV lipodystrophy, diabetes, bone fracture recovery, retinopathy of prematurity, and severe insulin resistance. Over 500 patients have been exposed to IPLEX, most at doses between 0.5 and 2 mg/kg/day. Positive effects on statural growth, insulin sensitivity, glycemic control, dyslipidemia, muscle strength, endurance, and functional abilities have been demonstrated.

In the Italian EAP, IPLEX is administered daily by subcutaneous injection. A majority of the patients initiated treatment at a dose of 1 vial per day (36 mg/day), which equates to approximately 0.5 mg/kg/day. Over time, doses in most patients have been escalated to approximately 1 mg/kg/day.

DISPOSITION AND DURATION

To date, 110 patients have enrolled in the EAP and received at least one dose of IPLEX in the Program. Disposition of patients is outlined in Figure 1.

Figure 1. Disposition



DEMOGRAPHICS

Demographic characteristics of patients prior to initiation of treatment in the EAP are summarized in Table 1.

Table 1. Demographics

number of patients	110
age (yr, mean ± SD)	56.6 ± 11.0
gender male female	 70 40
weight (kg, mean ± SD)	67.7 ± 14.4
pre-treatment ALSFRS-R mean ± SD (range)	 27.8 ± 8.0 (3 - 45)
site initial symptoms limb bulbar unknown	 86 21 3
time from first symptoms to diagnosis (months, mean ± SD)	12.3 ± 10.8
time from first symptom to treatment (months, mean ± SD)	37.9 ± 21.7

The patients participating in the Program are similar to ALS patients in published clinical trials in terms of pre-treatment age, time from first symptom to diagnosis, gender distribution, and site of symptom onset.[1,2] However, disease progression is much more advanced in patients receiving IPLEX compared to published clinical trial populations as evidenced by a longer time from first symptom to the start of investigational treatment (37.9 months in EAP patients vs. <2 years in the literature) and a corresponding lower pre-treatment ALSFRS-R (27.8 in the EAP patients vs. ~40 in the literature). As the progression of ALS typically leads to death within 3 to 5 years, many of the patients entering the Program are at a very advanced stage of the disease.[3]

SUMMARY OF RESULTS

Disease Progression

The revised ALS Functional Rating Scale (ALSFRS-R) is the predominant measure of disease progression reported by physicians in the EAP. The ALSFRS-R is an easily administered, 48-point rating scale used to document the patient's assessment of physical capability and independence in functional activities typically affected by ALS.[4] The scale is robust, with low inter- and intra-rater variability and proven validity across method of administration.[5] It has been reported to correlate with patient-perceived clinical function and to be predictive of survival.[4,6]

ALSFRS-R data for patients who successfully completed 12 months of treatment in the EAP and have both pre-treatment and 12-month ALSFRS-R values are provided in Table 2.

Table 2. ALSFRS-R Summary

N	Pre-Treatment ALSFRS-R	ALSFRS-R at 6 months	ALSFRS-R at 12 months
24	30.2 ± 7.9	27.8 ± 8.2	25.2 ± 7.8

In the patients summarized above, the ALSFRS-R decline from pre-treatment through last available ALSFRS-R value is 0.38 points per month. In 25% of these patients, on-treatment ALSFRS-R values either did not change over time or slightly increased.

To date, 54 patients have been treated for at least 6 months and have both pre-treatment and 6-month ALSFRS-R values. In this cohort, pre-treatment ALSFRS-R is 30.0 ± 7.9, 6-month ALSFRS-R is 25.7 ± 9.6, and the ALSFRS-R decline from pre-treatment through the last available ALSFRS-R value is 0.68 points per month. In 20% of these patients, on-treatment ALSFRS-R values did not change over time or slightly increased.

Safety

Five patients have discontinued from the EAP due to adverse events considered by the treating physician to be possibly related to IPLEX therapy. These events were one case of non-serious muscle twitching, one fatal case of cholelithiasis and infection following gallstone surgery in a patient with a history of gallbladder inflammatory disease, and three fatal events of cardio-circulatory arrest, one in a patient with a history of hypertension and silent myocardial infarction. An additional 30 patients have died, and the events were considered unrelated to IPLEX. In 29 of these 30 patients, death was caused by disease progression (cardio- or respiratory-failure); the remaining death was caused by suicide.

Of the 110 patients enrolled in the Program, 34 patients have died. These deaths occurred a median of 36 months from first ALS symptom, which is consistent with expected disease progression.[3] It is noted that 35% of these patients died prior to the completion of 3 months of IPLEX therapy.

CONCLUSIONS

To date, IPLEX has been generally well tolerated and there have been no safety concerns associated with IPLEX. Most of the patients enrolled into the Program are at an advanced stage of disease and a number of patients have died while on IPLEX, but these have been attributed by their physicians to disease progression. It is difficult to interpret the changes of ALSFRS-R scores observed in the remaining population because the Program does not have a concurrent control group.

REFERENCES

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